NAVAL HEALTH RESEARCH CENTER

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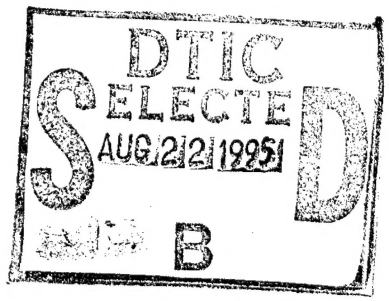

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NAVAL HEALTH RESEARCH CENTER
P. O. BOX 85122
SAN DIEGO, CALIFORNIA 92186 – 5122

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
BETHESDA, MARYLAND

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T. L. Kelly[1]
S. A. Gomez[2]
D. H. Ryman[1]
K. Schlangen[1]
T. Elsmore[3]

[1] Naval Health Research Center
P. O. Box 85122
San Diego, CA 92186-5122

[2] Commander Naval Surface Force
United States Pacific Fleet
San Diego, CA 92155-5490

[3] Walter Reed Army Institute of Research
Washington, D.C. 20307-5100

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SUMMARY

Problem - Emergency situations or sustained operations can require personnel to work for extended periods with little chance for sleep. This can impair alertness and performance. While powerful stimulants improve alertness and performance, most of such agents present a risk of addiction or side effects. Pemoline (Cylert™) may be an effective stimulant with no risk of addiction. Results of a previous study (Babkoff et al., 1992) suggest that pemoline is beneficial, but that repeated doses may have detrimental effects on some types of cognitive performance.

Objective - The present study investigated whether a single dose of pemoline could enhance performance in sleep deprived subjects.

Approach - Fourteen volunteers participated in a double-blind study. Subjects received placebo the first night and either 37.5 mg of pemoline or placebo during the second night of two sequential nights of sleep deprivation. A computer-administered Performance Assessment Battery of 11 cognitive tasks was administered every 3 hr. Performance data from the 10 hr following the initial placebo administration and during the 10 hr following drug administration were analyzed.

Results - In three of the tasks, pemoline reversed the cognitive decrement produced by sleep loss. Pemoline administration maintained performance on these tasks at levels similar to those the previous night of testing. Further, there was no evidence of any detrimental effects of pemoline on performance in this single-dose protocol.

Conclusion - Pemoline appears to be a promising agent for operational use. Further testing would be useful to determine the optimal dose.

INTRODUCTION

A number of previous studies have administered stimulants to try to improve various aspects of performance and/or mood. Historically, the German armed forces during World War II experimented with various stimulants (e.g., caffeine, phenylmethylamines, and benzedrine) in controlled sleep-deprivation studies (Graf, 1971). Those studies found that subjects experienced decreased fatigue and sleepiness, increased alertness, enhanced imagination, and euphoria. However, they also showed loss of inhibitions and decreased ability to concentrate. Laboratory studies of amphetamines have demonstrated improved performance in fatigued subjects (e.g., Holliday & Devery, 1962; Newhouse, Belenky, Thomas, Thorne, Sing, & Fertig, 1989).

Stimulants have been used to try to maintain performance during military operations. U.S. soldiers in Vietnam on reconnaissance patrols requiring long range or sustained activity were sometimes issued methylphenidate (Ritalin™) or dextroamphetamine (Jones, 1985). During the period between 1966 and 1969, the U.S. military consumed more amphetamines than the entire British and American armed forces during World War II (Mendleson, 1985). This trend has continued into the late 1980s and the 90s. Some pilots as well as support crews were reportedly using amphetamines to maintain alertness and performance during combat and support missions in both the Desert Shield and Desert Storm operations (Emonson & Vanderbeek, 1995).

Significant physical and psychological disadvantages may be associated with using these pharmacological agents to maintain alertness. Amphetamines can be abused and can induce physiological and psychological dependency (Mendleson, 1985). Other physical and behavioral effects can include arrhythmias, increased blood pressure, accelerated respiration, excessive weight loss, sleep disruption, excessive mood swings, anxiety, or even psychosis (Lowinson, Ruiz, & Millman, 1992; Morey, 1989; Mendleson, 1985). Although studies have shown that amphetamine users perform better on tasks that are tedious and simple in nature (Mendleson, 1985), performance on higher level cognitive tasks can be adversely affected. Studies by the Germans in World War II (Graf, 1971) showed that the working speed of subjects administered benzedrine increased on simple problems but decreased on more complex problems. Increased speed was also associated with an increase in the number of errors. An alternative pharmacological agent, which has stimulant properties without any known euphoric side effects or abuse potential, is the oxizolidine compound pemoline (Cylert™). Pemoline is used medically to maintain alertness in narcoleptics and to correct attention deficits in hyperactive children. Previous work by our laboratory (Babkoff et al., 1992; Matteson et al., 1990; Naitoh et al., 1990) showed that subjects who received 37.5 mg of pemoline every 12 hr during a 64-hr continuous work period showed reduced levels of objective and subjective sleepiness, without any effects

on mood. Pemoline treatment also maintained better performance in some tasks as compared to placebo treatment. In almost every task, speed improved. The benefits were most dramatic during the period of the circadian nadir. However, accuracy effects varied. Tests of pattern recognition and short-term memory showed no accuracy effects. There was significantly improved accuracy on the Four-Choice Reaction Time task with pemoline, and the Digit Symbol Substitution Task showed a trend for a similar improvement. However, significantly lower accuracy on Logical Reasoning was seen in the pemoline group during the second night of testing. Performance on the Addition task also showed a trend for decreased accuracy with pemoline late in the study. These negative effects may be related to accumulated blood levels after several repeated doses.

Since the greatest drug effects on sleepiness and performance were observed during the circadian low periods, and because repeated doses may have a negative impact on some performance measures, the present study was designed to investigate the impact of a single dose of pemoline administered during the second of two nights of sleep deprivation. This timing was selected to achieve maximum drug effects at the time when sleep deprivation and circadian variation would be expected to produce the worst performance decrements.

METHODS

Subjects

Fourteen male students from the Naval Training Center and the Naval Medical Center, San Diego, California, volunteered to participate in this study. The subjects' ages ranged from 18 to 21 (mean age = 19 years). They were non-tobacco users, no more than moderate caffeine users, and considered themselves to be from average to good sleepers. Selected medical history information revealed that the subjects were in excellent physical and psychological health. All subjects gave informed consent after receiving a detailed explanation of the protocol, which had been approved by the Naval Health Research Center Committee for the Protection of Human Subjects.

Procedures

The subjects were randomly assigned to either the control group ($\underline{N} = 7$) or the 37.5-mg pemoline group ($\underline{N} = 7$). Two to four subjects at a time participated in the 4-day protocol during which subjects went without sleep for 64 hr starting at wake-up 0600 the morning of Day 2. All

subjects received placebo capsules on Night 2, after 15.5 hr without sleep. On Night 3, after 39.5 hr without sleep, the experimental subjects received 37.5 mg of pemoline and the control subjects received a second matched placebo capsule. The experiment was double-blinded regarding the assignment of subjects to treatment groups. It was single-blinded for the administration of placebo capsules the first-night (i.e., subjects did not know whether these were active or placebo but experimenters knew all first night capsules were placebo).

During the study, the subjects remained in the laboratory but were allowed to go outside briefly during breaks. Meals and nighttime snacks, roughly equivalent in nutritional and caloric value, were provided to all subjects. However, subjects were allowed to consume additional snacks during their breaks and were not required to eat all their food at mealtime, so food consumption varied. Subjects were not allowed to consume food from 2 hr before to 1 hr after medication administration. No coffee, tea, caffeinated soft drinks, or chocolate were allowed during the study. Table 1 summarizes the experimental schedule.

A Performance Assessment Battery (PAB) administered on IBM-compatible, Intel/386-cpu computers was used to measure pemoline effects on cognitive performance. PAB testing was conducted in a soundproof testing room under standard low-level artificial lighting. Subjects worked at individual computers separated from each other by partitions. Experimenters were present in the testing room, ensuring that the subjects remained awake and worked on the tasks at all times. The PAB tasks are described in the appendix.

Vital signs

Vital signs [diastolic blood pressure (DiaBP), systolic blood pressure (SysBP), pulse, and temperature] were recorded every 2 hr. A Critikon Dinamap™ (Johnson & Johnson) vital signs monitor was used to record DiaBP, SysBP, and pulse measurements. Concurrently, temperature was recorded with an oral, basal-temperature thermometer.

Analysis

Three subjects were excluded from data analyses due to illness, decongestant injestion, and/or experimental error. In addition, review of the PAB data revealed a placebo subject who was an extreme outlier and performed very poorly over the entire study. His data were eliminated from the analysis of performance data but, were included in the analysis of the vital signs data (i.e., temperature, pulse, diastolic and systolic blood pressure) because he was not an outlier for

Table 1: Schedule

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
00-01		Sleep	Snack	Snack	Recovery Sleep
01-02			Tasks/VS	Tasks/VS	
02-03					
03-04			Free	Free	
04-05			Tasks/VS	Tasks/VS	
05-06					
06-07		Wakeup/Brkfst	Breakfast	Breakfast	Shower/Brkfst
07-08		Tasks/VS	Tasks/VS	Tasks/VS	Tasks/VS
08-09	Check-in				Debrief/ Released
09-10	Task Training	Free	Free	Free	
10-11		Tasks/VS	Tasks/VS	Tasks/VS	
11-12					
12-13	Lunch	Lunch	Lunch	Lunch	
13-14	Task Training	Tasks/VS	Tasks/VS	Tasks/VS	
14-15					
15-16		Free	Free	Free	
16-17		Tasks/VS	Tasks/VS	Tasks/VS	
17-18	Free				
18-19	Dinner	Dinner	Dinner	Dinner	
19-20	Free	Tasks/VS	Tasks/VS	Tasks/VS	
20-21					
21-22					
22-23	Sleep	Med*/Break	Med*/Break	Break/VS	
23-24		Tasks/VS	Tasks/VS	Recovery Sleep	

Med* = Medication (Placebo or Pemoline)
BLT = Baseline Tasks
Tasks = Performance Tasks
Free = Break between Tasks
VS = Vital Signs

Tasks/VS = Performance Task/Vital Signs used in Analysis

those measures. Thus, there were 11 subjects in the PAB analyses (6 pemoline and 5 placebo) and 12 subjects in the vital sign analyses (6 pemoline and 6 placebo).

The predrug (Sessions 1-15) performance data were subjected to a mixed design, repeated measure Analysis of Variance (ANOVA) to detect any baseline or post-placebo group differences, with Group as the between subjects factor and Session as the within subjects (repeated measure) factor. To test for drug effects over time, mixed design ANOVAs were performed with Group as the between subjects factor, and Session and Day as within subjects factors, looking at the first four sessions after initial placebo administration (Sessions 8-11, Day 1) and the first four sessions after administration of the second capsule (Sessions 16-19, Day 2). These sessions extend from 22:45 to 09:20 each day, including the usual circadian low point in performance (04:00-06:00). Post-hoc t-tests were done for any task measure showing significant interaction effects.[a]

A few sporadic extreme scores occurred, where subjects suddenly decreased their number of responses to less than half or increased the number to more than twice their response rate on the same task in earlier and later sessions on the same day. The Experimenter Log Book indicated several reasons for these occurrences: the subjects had difficulty remaining awake, computers malfunctioned, or subjects appeared unmotivated and took breaks during a task. Where these extreme scores occurred, a second analysis substituting the mean of the other sessions for the extreme scores was done to verify that significant results were not due to extreme scores alone, and that extreme scores did not obscure significant findings. For most measures, these substitutions did not affect results. Where there was any change, the results of both analyses are presented. Extreme scores occurred in a similar number of subjects from each group.

RESULTS

Predrug analysis

The two-way (Group x Session) ANOVAs of Sessions 1-15 showed only one measure (VAS Tension scale, $F(1,9) = 9.93$, $p \leq .01$) with a significant difference between the groups prior to drug administration. The group that later received pemoline had significantly higher Tension scale scores. The postdrug ANOVA of this variable was adjusted for this initial Tension difference. Almost all measures showed a main effect for Session and Days. Variation due to learning-related improvements in the early sessions, sleep deprivation in the later sessions, and

[a]Five vital sign measurements were included in each of these time periods (and in the analyses) because vital signs were taken at 2-hr intervals while performance was tested at 3-hr intervals.

circadian rhythms across all of the sessions probably contributed to these Session effects. Day differences showed worse performance the second day probably due to extended sleep loss.

Postdrug analysis

The results of the 3-way ANOVAs group difference effects are summarized in Table 2. Since the focus of the study was the effects of the drug, post-hoc testing will not be presented for main and interactive effects not involving Group.

Matrix. There was a main effect of Day [$F(1,9) = 9.20$, $p \leq .01$] for accuracy, with lower scores the second day, and a Day x Group interaction [$F(1,9) = 5.07$, $p \leq .05$], with the Pemoline group performing in the same range both days, and the Placebo group markedly lower the second day (see Figure 1). Post-hoc, independent t-tests indicated that the Placebo group had significantly decreased accuracy [$t(4) = 4.68$, $p = .009$ between Sessions 8-11 and 16-19], whereas the Pemoline group remained the same [$t(5) = .50$, $p = .50$]. The 16th session showed the largest difference between the groups [$t(9) = 2.78$, $p = .02$]. There were too few lapses to analyze, and the throughput results were virtually identical to those for accuracy for both ANOVA and post hoc tests.

Addition. There was a Day x Group interaction for accuracy [$F(1,9) = 5.50$, $p < .04$], which is shown in Figure 2. Three subjects had one extreme score during Sessions 8-11. Reanalysis with substitution of the means of the other sessions for the extreme scores showed similar significance [$F(1,9) = 8.12$, $p < .04$], with the Placebo group doing 17.3% worse Sessions 16-19 [$t(9) = 2.70$, $p < .02$], while the Pemoline group decreased only 2.7%. The most significant between-groups difference occurred during Session 16, the session following the pemoline/placebo administration [$t(9) = 2.02$, $p < .05$].

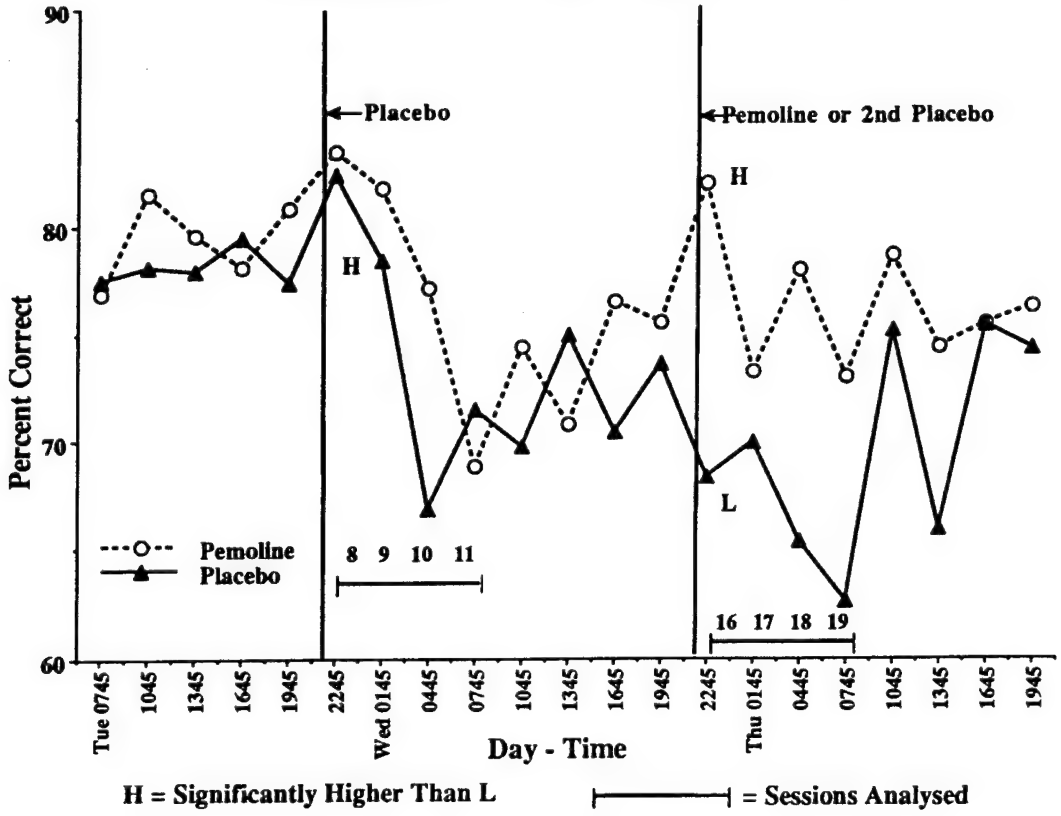
There was a main effect of Day [$F(1,9) = 26.21$, $p < .001$] and a Day x Group interaction [$F(1,9) = 12.52$, $p < .006$] for throughput (TP). Performance of the Placebo group declined significantly from Sessions 8-11 to Sessions 16-19 [$t(4) = 6.13$, $p = .004$]. However, performance of the Pemoline group remained about the same [$t(5) = 1.14$, $p = .31$]. These results may have been due to extreme scores, because when the extreme scores were removed the Day x Group interaction was not significant [$F(1,9) = 2.02$, $p = .19$]. The reaction time (RT) analysis showed only a Session effect [$F(3,27) = 4.66$, $p = .009$] and a Day x Session interaction [$F(3,27) = 3.21$, $p = .04$], but no Group-related effects.

Table 2. 3-Way ANOVA Group Factor Results.

TASK	Meas.	Group		Group x Day		Group x Sess		Group x Day x Sess	
		Fg	p	Fgd	p	Fgs	p	Fgds	p
Matrix	PC	4.20	.07	5.07	.05	1.16	.34	1.36	.30
	TP	4.18	.07	5.07	.05	1.17	.34	1.30	.30
Addition	PC	3.58	.09	5.50	.04	.11	.95	.42	.74
	RT	.05	.84	.18	.68	.08	.97	1.70	.19
	TP	.99	.35	12.52	.006	1.21	.33	.12	.95
Logic Simple	PC	2.59	.15	.30	.60	1.04	.40	.03	.99
	RT	.16	.70	11.54	.008	2.67	.13	.72	.55
	TP	1.40	.27	4.42	.07	1.08	.37	.25	.86
SRT	RT	.09	.77	.51	.49	1.12	.36	1.14	.35
CRT	PC	.01	.94	.02	.90	.58	.62	.98	.42
	RT	.02	.91	.40	.54	2.06	.13	.98	.42
	TP	.01	.93	.08	.79	1.09	.37	.21	.87
Four Choice	PC	.11	.75	.16	.70	.03	.99	1.32	.29
	RT	.03	.87	2.50	.15	.64	.60	1.60	.21
	TP	.03	.88	3.34	.10	.19	.90	3.68	.02
Digit Substitution	PC	.00	.95	1.75	.21	.48	.70	.59	.63
	RT	2.26	.17	2.17	.18	1.00	.41	1.04	.40
	TP	.01	.93	4.05	.07	1.46	.25	1.51	.24
Logic Complex	PC	.51	.50	.03	.86	.78	.52	3.91	.02
	RT	.01	.95	.90	.37	1.33	.29	1.60	.21
	TP	1.85	.21	.91	.37	.57	.64	5.53	.004
Word Memory	PC	.05	.83	1.89	.21	2.27	.11	2.32	.10
	RT	.00	.97	1.50	.28	.81	.51	.63	.61
	TP	3.32	.10	3.62	.09	.04	.99	.75	.41
Tapping Task	RT	3.16	.11	.07	.80	1.76	.18	.56	.64
	Lapses	.42	.53	7.12	.03	.92	.44	.51	.68
Synwork	Overall	.99	.34	1.34	.32	1.53	.23	1.02	.40
VAS	Sleep	8.82	.02	3.48	.10	2.02	.14	.83	.49
	Tense	10.2	.01	.29	.60	1.11	.36	3.00	.05
Vital Signs	Sys BP	.13	.73	.01	.92	1.08	.38	.25	.91
	Dia BP	1.94	.20	.13	.72	.88	.48	.43	.79
	Pulse	.00	.96	1.53	.25	.77	.55	1.41	.25
	Temp.	.01	.91	2.66	.14	.12	.98	.83	.52

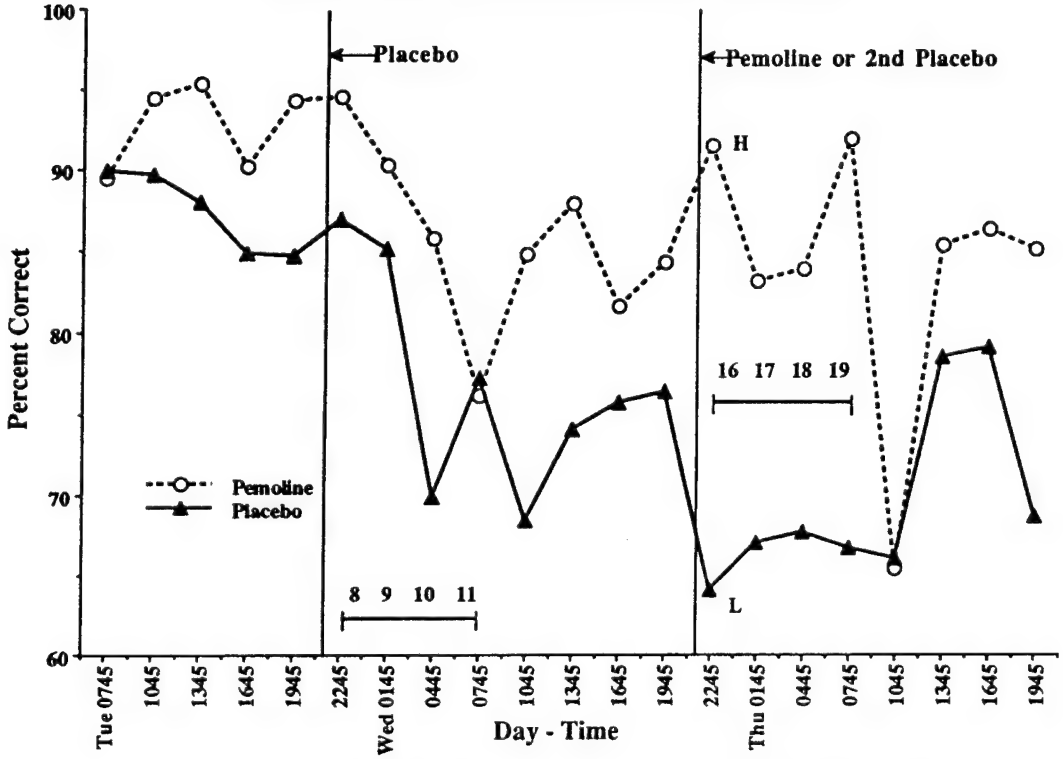
PC = percent correct, RT = reaction time, TP = throughput, SRT = simple reaction time, CRT = complex reaction time, VAS = visual analog scale

Fig. 1. MATRIX PERCENT CORRECT PEMOLINE AND PLACEBO GROUPS



H = Significantly Higher Than L ——— = Sessions Analysed

Fig. 2. ADDITION PERCENT CORRECT PEMOLINE AND PLACEBO GROUPS



H = Significantly Higher Than L ——— = Sessions Analysed

Logic (simple). The accuracy analysis showed only an effect for Session [$F(3,27) = 3.98$, $p = .02$]. There was a main effect of Day [$F(1,9) = 26.48$, $p < .001$] for TP and a near significant trend for a Day x Group interaction [$F(1,9) = 4.42$, $p < .06$]. The Pemoline group showed less of a decrement between Day 1 and Day 2 [$t(5) = 3.85$, $p = .01$] than the Placebo group did [$t(5) = 5.66$, $p = .005$].

There was a significant Day x Session x Group interaction for RT [$F(3,27) = 4.21$, $p < .02$]. Two different subjects each day had one extreme RT session score, where they produced either very few responses that were highly accurate or numerous responses of low accuracy creating very slow or very fast RTs. When means of the other sessions were substituted, there was a significant Day x Group interaction for RT [$F(1,9) = 11.54$, $p < .008$], with the Placebo group increasing more in RT (becoming slower) from Day 1 to Day 2 in comparison to the Pemoline group [$t(9) = 3.30$, $p = .008$]; no individual sessions were significantly different between groups. The Day x Session x Group interaction was not significant when the day mean was substituted for the extreme scores [$F(3,27) = 1.46$, $p < .24$]. Reanalysis of PC and TP without the extreme scores did not change the results.

Simple Reaction Time Task. There was a Day effect [$F(1,9) = 7.40$, $p < .02$] and a Day x Session interaction [$F(3,27) = 4.26$, $p < .01$] for RT (the only measure for this task), but there were no Group effects.

Complex Reaction Time Task. There were Session and Day x Session effects for accuracy [$F(3,27) = 3.66$, $p < .03$; and $F(3,27) = 4.52$, $p = .01$; respectively] and TP [$F(3,27) = 10.19$, $p < .003$; and $F(3,27) = 4.25$, $p = .03$; respectively]. RT showed only a Session effect [$F(3,27) = 3.86$, $p < .02$]. There were no effects of Group in any of the analyses.

4-Choice Reaction Time Task. There were no significant effects for accuracy. There were main effects for Day [$F(1,9) = 7.96$, $p < .02$] and Session [$F(3,27) = 9.09$, $p < .001$], and Day x Session [$F(3,27) = 7.89$, $p < .002$], and Day x Session x Group [$F(3,27) = 3.68$, $p < .04$] interactions for TP, which is shown in Figure 3. Both the Placebo and Pemoline groups made fewer correct responses in the first session after drug/placebo (Session 16) compared to the same session Day 1 (Session 8). In the next session (Session 17), only the Placebo group performed worse than on Day 1 [$t(4) = 3.70$, $p = .02$]. The Pemoline group performed better during the fourth session after drug administration [$t(4) = -3.16$, $p = .03$] than during the corresponding session on the previous day. Substitution of means for the few extreme scores did not change any of the above results. Only a Session effect [$F(3,27) = 9.09$, $p < .001$] was seen for RT.

Digit Symbol Substitution Task. There was a Day effect [$F(1,9) = 8.75$, $p < .02$], and a Day X Session interaction [$F(1,27) = 6.48$, $p < .002$] for TP, but there were no Group-related effects. There were no significant effects for accuracy or RT.

Logic (Complex). The only significant effect in the analyses of any of the measures was a Session effect [$F(3,24) = 3.54$, $p = .03$] for accuracy. There were no Group effects. One placebo subject apparently began guessing during Sessions 16-19, and another did very few problems (< 4 in 10 min) during these sessions. Other subjects showed apparent guessing or very slow responses during one of the sessions. These response patterns produced opposite effects. Guessing subjects showed many responses (quick reaction times) but low percent correct. Very slow responders showed long reaction times, but high percent correct. Reanalysis substituting means for the extreme sessions showed only a Day x Session x Group interaction [$F(3,27) = 5.53$, $p < .004$], with the Placebo group significantly worse than the Pemoline group only at the 17th session [$t(9) = 3.08$, $p = .01$].

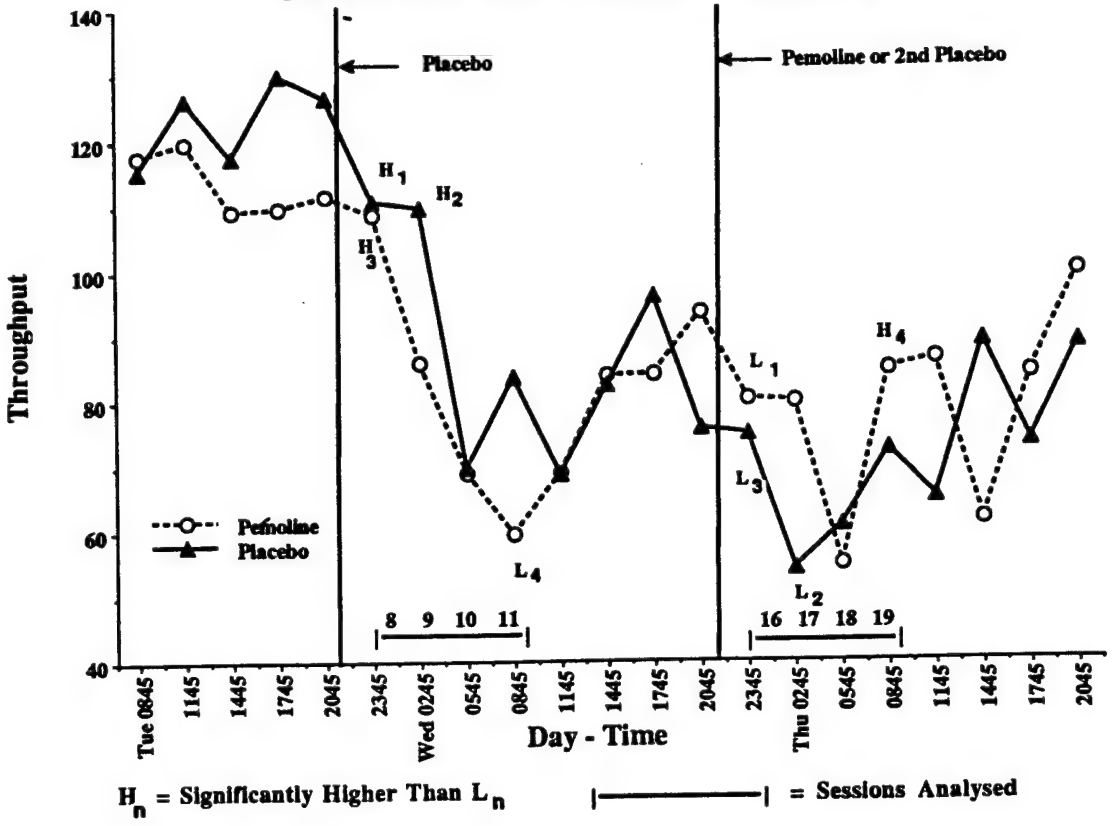
Word Memory. There were Session effects for accuracy [$F(3,27) = 3.54$, $p < .03$] and RT [$F(3,27) = 3.19$, $p < .04$]. No Group differences were found for any measure. There were no significant effects for TP.

Synthetic Work. There was a Session effect [$F(3,27) = 5.44$, $p < .005$] for the overall score, but there were no Group-related effects.

Tapping Task. There was a Day x Group interaction [$F(1,9) = 7.12$, $p < .03$] for number of lapses per session (see Figure 4, note that higher scores indicate worse performance in this graph) with the Placebo group increasing (tripling) from Sessions 8-11 to 16-19 [$t(4) = -3.50$, $p = .03$] while the Pemoline group remained the same [$t(5) = .10$, $p = .93$]. Post-hoc testing showed a significant difference between groups for session 17 [$t(9)=-2.22$, $p = .05$].

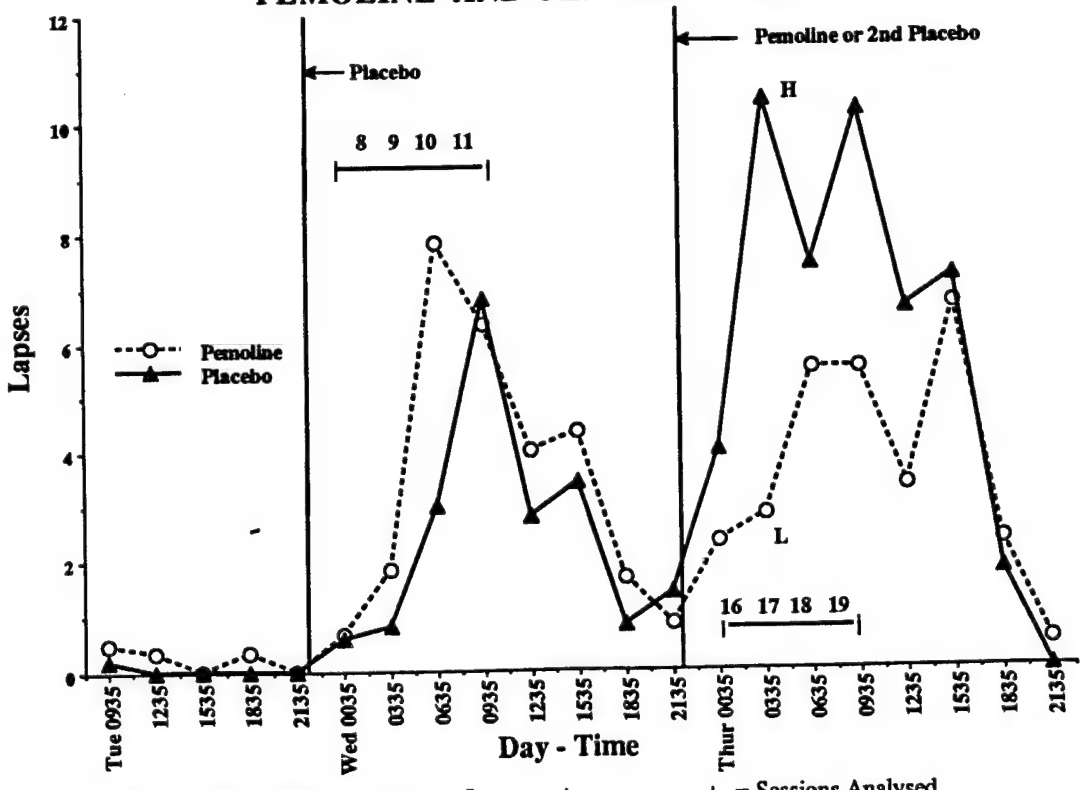
Visual Analog Scale. Significant Group differences were found for two of the scales, Sleepiness and Tension. There was a significant main effect of Group for the Sleepiness scale [$F(1,9) = 7.16$, $p = .03$]. Sleepiness was significantly higher for the Placebo group than for the Pemoline group during the second day sessions [$t(8) = 2.79$, $p = .002$], particularly for session 16 [$t(9) = 4.49$, $p < .002$]. The first day, sleepiness was not significantly higher in the Placebo group [$t(8) = 1.62$, $p = .15$]. However, there was only a trend for a Day x Group interaction [$F(1,9) = 3.48$, $p = .10$]. When we adjusted for baseline differences on the Tension scale, that analysis showed no significant effects.

Fig. 3. FOUR CHOICE THROUGHPUT PEMOLINE AND PLACEBO GROUPS



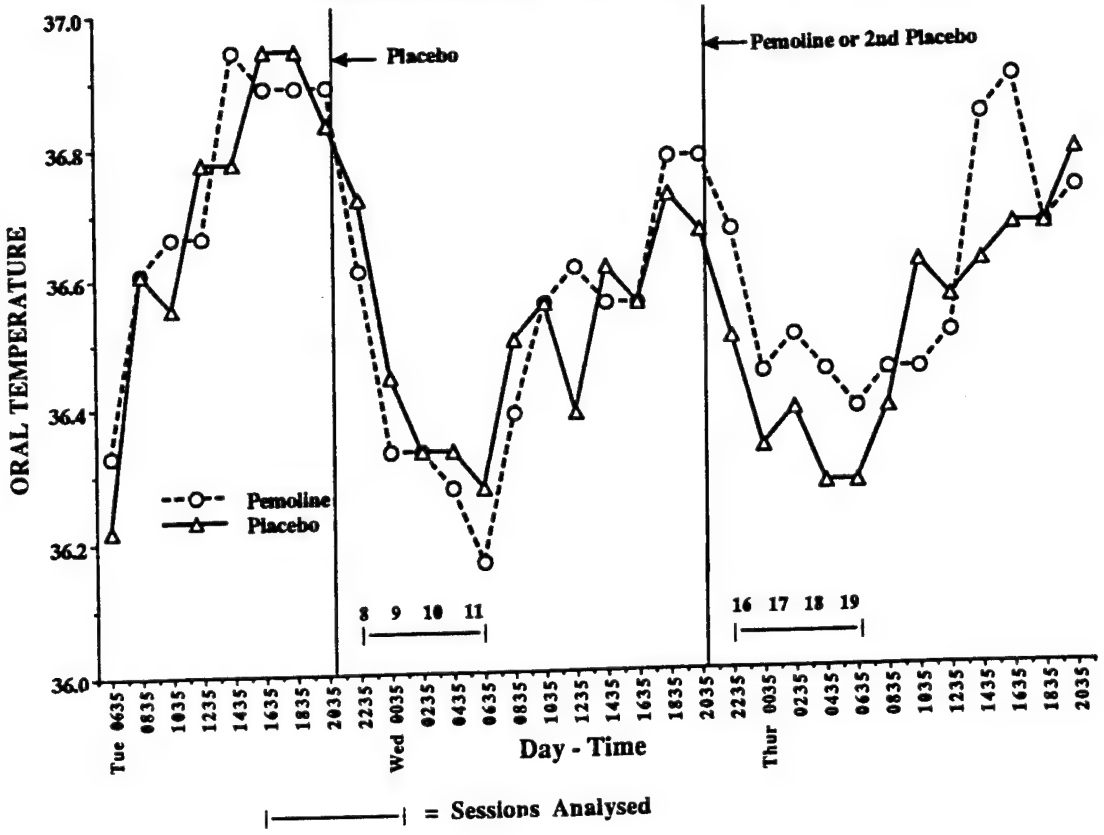
H_n = Significantly Higher Than L_n |——| = Sessions Analysed

Fig. 4. TAPPING LAPSES PEMOLINE AND PLACEBO GROUPS



H = Significantly Higher Than L |——| = Sessions Analysed

Fig. 5. ORAL TEMPERATURE
PEMOLINE AND PLACEBO GROUPS



Vital Signs

There were no significant effects in the analyses of the vital signs data. The peaks and valleys of temperature are timed very closely with those of performance (see Figure 5).

DISCUSSION

In this study, a single dose of pemoline administered prior to the last 24 hr of a 64-hr period of sleep deprivation significantly lowered objective sleepiness, as measured by lapses on a tapping task. There is a trend for decreased subjective sleepiness as well. Subjects who received pemoline also showed improved accuracy of performance on the Matrix and Addition tasks, relative to the group that received placebo. A similar improvement was found in throughput on the Matrix task and the Addition task, although the Addition findings are somewhat suspect because they disappeared in a reanalysis excluding extreme findings. Subjects in the Pemoline group performed better than those in the Placebo group for some postdrug sessions, but the

pattern was less uniform (Figure 3). A near significant trend for better throughput on the simple version of the Logic task was also seen with pemoline. For all the measures showing Day x Group interactions, the Placebo group performance was significantly worse at the 16th or 17th session (immediately postmedication) than on the preceding night (8th or 9th session), while the Pemoline group remained at about the same level of performance as the previous night. The only evidence of an effect on speed of performance (other than the throughput findings, which incorporate a speed aspect) was in the simple Logic task, where reanalysis excluding extreme scores found the subjects who received pemoline worked faster than those who received placebo (this finding was not seen on the unadjusted data). There was no evidence of negative effects with this drug at this dosage (37.5 mg).

In the predrug analyses, percent correct on all tasks varied significantly across sessions in accordance with circadian rhythm. In the graphs of the performance data it can be seen that decrements are more prominent the second night than on the first, and comparing Figure 5 with the performance graphs shows that the temperature nadirs tend to coincide with periods of worst performance in the Placebo group. This finding is consistent with the premise of Babkoff, Mikulincer, Caspy, and Sing (1992) that performance and temperature rhythms share the same oscillators and that oscillations become more prominent with sleep deprivation. However, for several of the variables, the second night's decrement is no greater than, or even smaller than, the first night's for the Pemoline group.

The literature suggests that stimulants enhance performance in tasks that are tedious or require rote learning (Peloquin & Klorman, 1986; Rapoport et al., 1980). The data from this study are consistent with this. Neither accuracy nor throughput (which encompasses an accuracy aspect) showed an effect of pemoline in the more complex tasks, such as the complex version of the Logic task and Digit Symbol Substitution task. However, on the simple tasks (i.e., Matrix, Addition, and Tapping) the subjects who received pemoline performed better.

The results from this single-dose administration are in marked contrast to our previous study of repeated pemoline administration (37.5 mg every 12 hr x 4 doses). The multiple-dose study demonstrated consistent improvement in speed on cognitive tasks, inconsistent effects on accuracy, and no effects on objective sleepiness (as measured by the Tapping task). Single-dose administration predominantly benefitted accuracy, improved speed on only one task (simple Logic), and decreased objective sleepiness. It is of particular note that the negative effects on accuracy (significant for simple Logic, with a trend for Addition) found with repeated pemoline administration are not seen with single dose administration. In fact, the data show a positive

effect of pemoline on Addition percent correct and a trend for a positive effect on simple Logic TP.

Stimulants have most often been reported to increase response speed on cognitive tasks, probably by affecting response selection rather than stimulus evaluation (Callaway, 1983). Thus, the finding of predominantly accuracy effects is unusual. The initial administration of pemoline at the circadian nadir after significant sleep deprivation may be important to this response pattern. Most previous studies have not used this administration schedule. Maintaining accuracy is probably more important to most operational goals than is maintaining speed. Thus, this pattern of administration may be preferable for operational use.

CONCLUSION

A single dose of pemoline administered during the second of two nights of sleep deprivation improved accuracy (percent correct or throughput) of performance, predominantly on simple rather than complex tasks. There were minimal effects on speed and no negative effects. Vital signs were unaffected by the drug. Administration of this and perhaps other stimulants at the time of maximum need (previous sleep deprivation added to the effects of the circadian low period for performance and alertness) may provide optimum effects. The results of this study suggest that pemoline is a promising stimulant for operational use. Further testing to confirm these preliminary results and determine optimum dose would be useful.

REFERENCES

Babkoff, H., Kelly, T. L., Matteson, L. T., Gomez, S. A., Lopez, A., Hauser, S., Naitoh, P., & Assmus, J. (1992) Pemoline and methylphenidate: Interaction with mood, sleepiness, and cognitive performance during 64 hours of sleep deprivation. Military Psychology, 4, 235-265.

Babkoff, H., Mikulincer, M., Caspy, T., & Sing H. C. (1992). Selected problems of analysis and interpretation of the effects of sleep deprivation on temperature and performance rhythms. In D. Friedman & G. Bruder (eds.) Psychophysiology and Experimental Psychology: A Tribute to Samuel Sutton, Vol 658, New York, Annals of the New York Academy of Sciences Publishers.

Baddeley, A. D. (1968). A three minute reasoning test based on grammatical transformation. Psychonomic Science, 10, 341-342.

Callaway, E. (1983). Presidential address, 1982 - The pharmacology of human information processing. Psychophysiology, 20, 359-371.

Emonson, D. L., & Vanderbeek, R. D. (1995). The use amphetamines in U.S. Air Force tactical operations during Desert Shield and Desert Storm, Aviation, Space, and Environmental Medicine, 66, 260-263.

Graf, O. (1971). Increase of efficiency by means of pharmaceutics (stimulants). USAF School of Aviation Medicine (ed.) German aviation medicine, World War II. Prepared under the auspices of the Surgeon General, U.S. Air Force. Pelham Manor, NY: Scholium International.

Holliday, A. R., & Devery, W. J. (1962). Effects of drugs on the performance of a task by fatigued subjects. Clinical Pharmacology and Therapeutics, 3, 5-15.

Jones, F. D. (1985). Sanctioned use of drugs in combat. In P. Pichot, P., Berner, R. Wolf, & K. Thau (eds.) Psychiatry; the state of the art, Vol VI, New York: Plenum Publishers.

Lukas, S. E. (1985). History of amphetamine use and abuse. In: S. H. Snyder (ed.) The Encyclopedia of Psychoactive Drugs Amphetamines, Danger in the Fast Lane. New York: Chelsa House Publishers.

Matteson, L. T., Kelly, T. L., Babkoff, H., Hauser, S., & Naitoh, P. (1990). Methylphenidate and pemoline: Effects on sleepiness and mood during sleep deprivation (NHRC Report No. 90-41).

San Diego, CA: Naval Health Research Center.

Morey, W. A., Dejohn, C. A., & Blackwell, O. G. (1989). Aeromedical consideration of stimulants in fleet operations and the development of pharmacological pretesting and education system. White paper for Naval Aerospace Medical Research Laboratory, Pensacola, Florida.

Naitoh, P., Kelly, T. L., & Babkoff, H. (1990). Napping, stimulant, and four choice performance (NHRC Report No. 90-17). San Diego, CA: Naval Health Research Center.

Newhouse, P. A., Belenky, G., Thomas, M., Thorne, D., Sing, H. C., & Fertig, J. (1989). The effects of d-amphetamine on arousal, cognition, and mood after prolonged sleep deprivation. Neuropsychopharmacology, 2, 153-164.

Peloquin, L. J., & Klorman, R. (1986). Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. Journal of Abnormal Psychology, 95, 88-98.

Rapoport, J. L., Buchsbaum, M. S., Weingartner, H., Zahn, T. P., Ludlow, C., & Mikkelsen, E. J. (1980). Dextroamphetamine: Its cognitive and behavioral effects in normal and hyperactive boys and men. Archives of General Psychiatry, 37, 933-943.

Thorne, D., Genser, S., Sing, H., & Hegge, F. (1985). The Walter Reed Performance Assessment Battery. Neurobehavioral Toxicology and Teratology, 7, 415-418.

Wilkinson, R. T., & Houghton, D. (1975). Portable Four-Choice reaction time test with magnetic tape memory. Behavior Research Methods and Instrumentation, 7, 441-446.

APPENDIX: PAB TASKS

The PAB comprised the following tasks, which are listed in the order of presentation:

1. **Matrix Task** (Matrix, Walter Reed PAB task [Thorne, Genser, Sing, & Hegge, 1985]). This is a spatial memory exercise involving pattern recognition and short-term memory. Patterns of 14 stars (asterisks) are presented for 2 s, and the subjects are instructed to remember the pattern. Following a 5-s blank screen delay, a second pattern appears, and the subject must determine whether it is the same or different from the first pattern. The second pattern of stars remains on the screen until the subject responds. Measures: Percent Correct (PC), Throughput (TP, number correct per unit of response time), and lapses (failure to respond within 60 s). Task duration was 10 min.

2. **Two-Column Addition Task** (Addition, Walter Reed PAB task). This task measures the ability to add five two-digit numbers arranged in a column. The task is dependent on ability to remember the sum of the right-most digits. The subject types in the answer on the numeric keypad. Measures: PC, Reaction Time (RT, average response time) and TP. Task duration was 10 min.

3. **Logic (simple)**. The Logical Reasoning task is a computerized variation of the Baddeley task (Baddeley, 1968). It measures the higher mental processes of reasoning, logic, the integration and manipulation of information, and verbal ability. This version of the task uses sequences of three letters (A, B, and C, in any order) paired with two logical statements, with the response being T (true) only if <u>both</u> statements correctly described the letter sequence. An example of this task is:

   CAB
   A does not precede B
   C does not follow B.

   Since the first statement is incorrect, and the second one is correct, the answer to this example is to press the "U" key (untrue). Half of the statements presented are true and half are false. Measures: PC, RT, and TP. Task duration was 20 min, with new problems appearing after every response or after 15 s with no response.

4. **Simple and Complex Reaction Time Task** (SRT and CRT). This task has two parts. In the SRT part, each trial starts with a blue square appearing in the center of the screen. The subject must depress a response key on the mouse and hold it until, after a variable interval, the square turns green, when the key must be released. In the CRT part, the trials start the same but the second color may be either green or red. When the square

turns green, the subject must release the key as quickly as possible. For red signals the subject must keep the key depressed for 1 s before releasing. Measures: only RT for SRT; PC, RT, and TP for CRT. The two parts of the task each lasted five min.

[There was a 10 min break between these first five tasks and the last five.]

5. **Four-Choice Serial Reaction Time Task** (Four Choice, Walter Reed PAB task). This task measures ability to track visual stimuli (Wilkinson & Houghton, 1975). The screen is divided by vertical and horizontal lines, and a star (asterisk) is displayed in one of the four quadrants of the screen. The response buttons representing the screen quadrants are arranged in a square (1,3,7,9 keys on the numeric keypad). The subject must press the response key whose position corresponds to that of the star with the index finger of the preferred hand, returning to the 5 key after each response. Each stimulus is displayed until the subject responds, after which the next stimulus is immediately displayed. Measures: PC, RT, and TP. Task duration was 11 min.

6. **Digit Symbol Substitution Task**. In this task the numbers 1 through 9 are displayed at the top of the screen, matched in random order with the symbols "!," "@," "#," "$," "%," "^," "&," "*," and "(." Numbers are presented one at a time in the lower portion of the screen. Subjects responded by pressing the numeric key that matched the symbol on the top row of the keyboard. The table of numbers and symbols remains on the screen constantly. Measures: PC, TP, and RT. Task duration was 5 min.

7. **Logic (complex)** (Logic, a variation of a Walter Reed PAB task). In this task, a letter sequence is displayed on the screen at the same time as a logical statement(s) about the order of the letters. There are 30 problems, 10 each at three levels of difficulty (a single logical statement combined with "AB" or "BA"; two statements combined with "A," "B," and "C" in any order [as for Logic (simple) above]; and three statements combined with "A," "B," "C," and "D" in any order). If all statements accurately describe the letter sequence, subjects type "T" for "true." If any statement does not describe the letter sequence, subjects type a "U" for "untrue." Measures: PC, RT and TP. Completing the 30 problems usually took subjects about 5 min.

8. **Word Memory Task**. On each trial, a list of 20 words is displayed for 10 s. Subsequently, 20 words (10 from the list and 10 distractors) are presented singly and in random order. The subject is allowed 20 s to respond before the next trial. The subject must respond "T" if he thinks the word was in the list and "U" if it was not. The task

consists of administration of six lists of 20 words. Measures: PC, RT, and TP. Duration was about 10 min.

9. **Synthetic Work Task (Synwork)**. This is composed of four different tasks presented simultaneously in the four quadrants of the screen. The subject must learn to maximize the overall score by apportioning time among the tasks. The components were selected to provide a generic office-type environment. All responses were given using the mouse, permitting the subject to concentrate on the information on the screen, and eliminating the distraction of locating a key on the keyboard or variability in the speed of response caused by differences in typing skills. Measure: A single overall score (see scoring below) summarized the performance on all four component tasks. Task duration was 15 min. The component tasks are:

   a. Sternberg Memory Task -- A list of six random letters is displayed at the top of the window for 5 s. Clicking the mouse on the RETRIEVE LIST box at any time re-displays the list for another 5 s. A random letter is displayed in the center of the window every 20 s. The subject responds by clicking the mouse in the YES or the NO box at the bottom of the screen to indicate whether the letter is included in the list. Ten points are awarded for each correct response, and deducted for each error.

   b. Arithmetic Task -- Two randomly selected numbers less than 1,000 are presented, with the answer 0000. The subject adjusts the answer by clicking on "+" and "-" boxes below each character of the answer. Clicking the DONE box at the bottom of the window causes a new problem to be presented. Ten points are awarded for each correct response or deducted for each error.

   c. Visual Monitoring Task -- A pointer moves from the center of a graduated scale toward either end at a fixed rate. Clicking the mouse on the RESET box at the top of the window resets the pointer to the center. The subject must prevent the pointer from reaching either end of the scale. Points awarded for each reset are proportional to the distance of the pointer from the center (10 points for most distant 10%, 9 for next most distant 10%, etc.). Ten points are deducted for each second the pointer is at either end of the scale.

   d. Auditory Monitoring Task -- A 5-s tone of either low or high frequency is sounded periodically. The subject is instructed to click the HIGH TONE

sounded periodically. The subject is instructed to click the HIGH TONE REPORT box at the top of the window following a high tone. High tones occur 20% of the time. A correct response given within the time limit accrues 10 points. All other responses result in the deduction of 10 points.

10. **Visual Analog Scale (VAS).** This is a measure of subjective mood. The VAS test consists of positioning a marker with the mouse on a line representing a 51-point continuum running between "VERY LITTLE" (0) and "VERY MUCH" (50) for the inquiries "How ALERT [SAD, TENSE, HAPPY, WEARY, CALM, SLEEPY] do you feel?" The same response scale is presented for the question "How much EFFORT is it to do anything?" Subjects respond within the continuum of "VERY BAD" to "VERY GOOD" to the question "OVERALL how do you feel?"

11. **Tapping Task.** This task measures ability to sustain attention to an easy task. The task requires tapping a key at a rate of once per second. "Lapses" in tapping are scored when subjects pause for more than 4 s between taps. When subjects pause for more than 4 s, the computer beeps, reminding them to resume tapping. Increase in numbers of lapses has been previously observed to correlate with shorter sleep latency as measured by the Multiple Sleep Latency Test (MSLT, Johnson, Spinweber, & Gomez, 1990). Thus, the tapping task measures both slowing due to sleep loss and objective sleepiness. Measure: lapses. Task duration was 5 min.

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13. ABSTRACT *(Maximum 200 words)* Sleep deprivation during SUSOPS can impair alertness and performance. Amphetamines are addictive drugs that can have significant side effects. A previous multiple dose study suggested that pemoline may provide an effective alternative to amphetamines, but that repeated doses may have detrimental effects on some types of cognitive performance. The present study investigated the effect of a single dose of pemoline administered at the time when sleep deprivation and circadian variation produce the worst performance decrements. Subjects received either placebo or 37.5 mg of pemoline during the second of two sequential nights of sleep deprivation. Cognitive performance testing occurred every 3 hr. Pemoline improved performance relative to placebo in three of the tasks, maintaining performance at the level seen on the first night of sleep deprivation. Pemoline appears to be a promising agent for operational use. Further testing is recommended to define the optimal dose.

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